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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/577,047	09/01/2006	Kazuyuki Ohmoto	Q94625	2314

23373 7590 09/10/2009

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EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
09/10/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/577,047	OHMOTO ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20060424, 20060901 & 20070316*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 12-20 are pending in this application.

Election/Restrictions

Applicant's election without traverse of Group I in the reply filed on May 28, 2009 is acknowledged. Applicant's election of the species of Example 5(2) is also acknowledged. As the elected species was not found in the prior art, the search was expanded to the elected invention of Group I.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 14, 19 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising a compound (having the formula depicted in claim 12) or a pharmaceutically acceptable salt thereof, does not reasonably provide enablement for a pharmaceutical composition comprising a solvate of the compound or prodrug of the compound. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The

nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

(A) The instant claims recite "A pharmaceutical composition comprising a compound ... a salt thereof, ... solvate thereof or a **prodrug** thereof" or "A method for prevention and/or treatment .... administering ... the compound .... formula (Ib-1) ... a solvate or a **prodrug** thereof", wherein the specification does not sufficiently provide enablement for the "prodrugs" or "solvates" of the instantly claimed compounds. The term "prodrug" is explained in the specification at page 27 as "a compound is the compound represented by formula (I) by reaction with enzymes, gastric acids and so on within an organism". While, the specification provides a generic definition for the term, does not provide what are some of the examples of such "prodrugs" intended by the definition provided in the specification. The claimed structural formula includes, for example, the term "substituent" is defined to include 'hydroxyl which may have substituents; carbamoyl which may have substituents; sulfamoyl which may have substituents; etc.', some of which can undergo solvolysis or hydrolysis. Since functional groups such as esters, amides, etc. are already included in the claimed compounds, it is not clear whether compounds bearing these groups are excluded from being a potential "prodrugs" of the claimed invention. If compounds bearing these groups (i.e., ester, amide, etc.), which are likely to undergo *in vivo* transformation, are excluded then what is included in the definition of the above term and where on the structural formula (I) are such groups placed; the specification does not provide any direction to one of ordinary skill in the art.

A prodrug as defined by Bundgaard (Design of Prodrugs) "is an inactive species, and therefore, once its job is completed, intact prodrug represents unavailable drug" (see page 1). Thus, an important requirement of prodrugs is that they be pharmacologically inactive. The scope of the term 'prodrugs' is quite broad. A state of the art reference, Silverman (The Organic Chemistry of Drug Design and Drug Action) teaches many strategies for making prodrugs. Among them are polymer-bound prodrugs (pages 369-374), acyclic prodrugs which form heterocyclic compounds *in vivo* (page 360), conjugates consisting of two or more drug molecules which are cleaved into active drug molecules (page 377), amine precursors which are converted to amines *in vivo* (page 358), and drugs bound to a carrier via a linker (page 374). Applicant has neither described nor provided working examples for the combination of the invention compound with various types of 'other compounds' or 'pharmaceutical excipients' intended by the instant claim language. In a clinical trial setting, it would require undue experimentation to determine whether a particular compound meets the criteria of a 'prodrug'.

(B) Further, the specification has no working example of "**solvate**" of compound of formula (Ib-1); and some of the exemplified compounds within the claimed genus were in contact with solvent. Yet they have not formed solvate as evident form spectral data provided for these compounds.

Searching the pertinent art in the related area of pyrimidines did not result in support for such solvates of compounds of instant structural formula. Searching the more general area of solvates resulted in pertinent reference West applied below. West clearly shows lack of predictability of the art in the solvate area.

Based on these two facts, a scope of enablement rejection follows using relevant Wands

factors. Hence, the burden of establishing the *prime facie* case is met with.

(i). **The nature of the invention and the state of the prior art:**

Specification is not adequately enabled as to how to make **solvate** of compounds of formula (Ib-1). Specification has no example of solvate of the instant compounds. The term 'solvate' generally refers to a complex variety of variable stoichiometry formed by a solute and a solvent and solvents include water, methanol, ethanol or acetic acid, but there is no enabling disclosure of such solvates in the instant specification.

The structural formula (Ib-1) embraces compounds having various variables, i.e., R^1, R^2, etc., and various substituents thereof. Careful calculation of the number of compounds embraced in the instant formulae shows a large number of compounds and there is no teaching of any solvate of this large genus.

Search in the pertinent art, including water as solvent resulted in a pertinent reference, which is indicative of unpredictability of solvate formation in general. The state of the art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is the compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometry of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. Compared

with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stabile region of the solvate. In the instant case of solvate a similar reasoning therefore applies. Water is a solvent and hence it is held that a pertinent detail of West, which relates to solvates, is also applicable to water.

In addition, an additional search resulted in Vippagunta et al., Advanced Drug Delivery Reviews 48: 3-26, 2001, which clearly states that formation of solvates in unpredictable. See entire document especially page 18, right column section 3.4. Note Vippagunta et al., states "Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for series of related compounds".

Joachim Ulrich (Kirk-Othmer Encyclopedia of Chemical Technology) provides that "Pseudopolymorphs are solvates or in the case of water as solvent, hydrates, which means crystals that incorporate solvent molecules into the crystal lattice. Pseudopolymorphs exhibit different crystal forms and/or different densities, solubilities, dissolution rates, colors, hardnesses, etc. Compared with polymorphs, there is an additional degree of freedom (than temperature and pressure), which means a different solvent or even the moisture of the air that might change the stabile region of the pseudopolymorph".

(ii). **The predictability or lack thereof in the art:**

Hence the solvate as applied to the above-mentioned compounds claimed by the applicant are not art-recognized compounds and hence there should be adequate enabling disclosure in the specification with working example(s).

(iii). **The amount of direction or guidance present:**

Examples illustrated in the experimental section are limited to making the compounds not

related to solvates. There is no example of solvate of instant compound. Many of the exemplified compounds were shown in the specification, that have come in contact with water and/or other solvent but there is showing that these compounds formed solvates. Hence it is clear that merely bringing the compound and water or solvent together does not result in solvate and additional direction or guidance is needed to make them - specification has no such direction or guidance.

(iv). **The presence or absence of working examples:**

There is no working example of any solvate formed. The claims are drawn to solvate, yet the numerous examples presented all failed to produce a solvate or even solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "[T]he specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there, is no evidence that such compounds exist... the examples of the patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, there should be showing supporting that solvates of these compounds exists and therefore can be made.

(v). **The breadth of the claims & the quantity of experimentation needed:**

Specification provides no support, as noted above, for compounds generically embraced in claim 12 would lead to desired solvate of the compound of formula (Ib-1). As noted above, the genus embraces a large number of compounds and hence the claims are extremely broad. The quantity of experimentation needed would be an undue burden on skilled art in the chemical art since

there is inadequate guidance given to the skilled artisan for the many reasons stated above. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired solvate of compound of formula embraced in the instant claims in view of the pertinent reference teachings.

2. Claims 15-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising a compound of formula (Ib-1) and a method of treating asthma, does not reasonably provide enablement for a pharmaceutical composition which is preventive and/or therapeutic agent for mitochondrial benzodiazepine receptor mediated disease generally; or a pharmaceutical composition which is a combination of the compound of formula (Ib-1) and an additional drug; or a method for prevention and/or treatment for a mitochondrial benzodiazepine receptor mediated disease generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the

claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant claims 15-19 are drawn to 'pharmaceutical composition which is preventive and/or therapeutic agent'. When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See MPEP § 2164.01(c). In contrast, when a compound or composition claim is **not** limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for non-enablement based on how to use.

The instant claim 19 is drawn to 'a pharmaceutical composition comprising a compound of formula (Ib-1) together with an additional drug selected from anxiety drugs, antidepressant drugs, etc.' and the specification does not provide sufficient written description regarding such combination compositions. The specification on pages 45-49 provides some examples of the additional substance of the composition intended by the instant claims, however, the scope of the claims includes agents that are known and those that may be discovered in future, for which there is no enablement. Specifically, the examples in the specification include generic groups or agents such as anxiety drugs, antidepressant drugs, antiparkinson drugs, etc. all of which include numerous species and there is insufficient guidance in the specification to enable one of ordinary skill in the art how the compounds of the invention and the other biological agent provide a synergistic activity to achieve the desired results.

The specification fails to enable one skilled in the art to use the instantly claimed compounds in a method for **prevention** and/or treatment of all types of diseases mediated by mitochondrial benzodiazepine receptor. The specification discloses that the compounds show

affinity to MBR and therefore, useful to treat a variety of diseases, see specification pages 43-44. Biological assays to test the activity of the compounds are provided on pages 28-29, and it is concluded that the compounds of the invention have affinity to MBR. However, the specification does not provide how this activity of affinity to MBR links to the treatment of all types of disorders (some of which are listed on pages 43-44) and there is no reasonable basis for assuming that the myriad of compounds embraced by the instant claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art (directed to nicotinic receptor binding agents) for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. Also, see MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally an unpredictable and highly structure specific area.

The scope of the claims is not adequately enabled solely based on the activity related to affinity to MBR provided in the specification. The claim language includes diseases that are known and those that are yet to be discovered, for which there is no enablement. First, the instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. The use disclosed in the specification is for the treatment of a laundry list of diseases caused by stress, which include all types of CNS diseases, respiratory system diseases, diseases of the digestive system, etc. Test assays and procedures are provided in the specification at pages 28-29, and it is concluded that the compounds of the invention display high affinity to MBR, however, there is nothing in the disclosure regarding how this data correlates to the treatment of the diverse disorders encompassed by the instant

claims. The disorders encompassed by the instant claims include central nervous system diseases, etc., some of which have been proven to be extremely difficult to treat. Regarding the pharmacology of MBR, a state of the art reference, Pelaia et al. (see the enclosed article) expresses that "The physiologic role of MBRs is still not well defined", see page 495. The reference further provides that: "The major problem arises from the nearly complete lack of knowledge about the signal transduction pathways and the effector systems coupled to MBR", see page 497. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Further, the instant claims include a variety of conditions which fall within the meaning of "central nervous system diseases" - which for example includes neurodegenerative diseases. In fact, Layzer, Cecil Textbook of Medicine (article enclosed), states that "some degenerative diseases are difficult to classify because they involve multiple anatomic locations" (see page 2050). For example, Alzheimer's disease has traditionally been very difficult or impossible to prevent or even to treat effectively with chemotherapeutic agents. See e.g., the Cecil Textbook of Medicine, 20th edition (1996), Vol. 2, wherein it is stated that "[t]here is no cure for Alzheimer's disease, and no drug tried so far can alter the progress of the disease." (pg. 1994).

The instant claim includes 'a method for prevention and/or treatment for a mitochondrial benzodiazepine receptor mediated diseases', however, applicant has not provided any correlation between nicotinic receptor binding activity and the instantly claimed therapeutic method. For

example, the instantly claimed preventive and/or therapeutic methods include the prevention and/or treatment of CNS diseases which includes Alzheimer's disease, which has traditionally been very difficult or impossible to prevent or even to treat effectively with chemotherapeutic agents. See e.g., the Cecil Textbook of Medicine, 20th edition (1996), Vol. 2, wherein it is stated that "[t]here is no cure for Alzheimer's disease, and no drug tried so far can alter the progress of the disease" (pg. 1994). It is known that antipsychotic medications are used to reduce the psychotic symptoms of schizophrenia. The state of the art of such antipsychotic drugs, however, indicates that 'they do not cure or restrain the symptoms of schizophrenia or ensure that there will be no further psychotic episodes'. The online information about the treatment options of the disease http://www.psychologyinfo.com/schizophrenia/medication-treatment.html indicates that 'it is difficult to predict which patients will benefit from treatment with antipsychotic drugs. Different patients have different treatment responses and side effects to various antipsychotic drugs', thus, clearly indicating the unpredictability in the dosage regimen.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

It is difficult to treat many of the disorders claimed herein. Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied on are reasonably predictive of *in vivo* efficacy by those skilled in the art. See for example *In re*

Ruskin 148 USPQ 221; *Ex parte Jovanovics* 211 USPQ 907. Applicant has not provided any reference(s) that forms sufficient evidence that claimed uses were art-recognized based on activity relied on at the time of applicants' effective filing date. MPEP 2164.05(a). When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. Tossing out the mere germ of an idea does not constitute enabling disclosure. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006.

The diagnosis of each of the disease is generally suggested by medical history and reports of endoscopy, cytology, X-ray, biopsy, etc. depending on the symptoms, signs and complications, which is essential to establish the dosage regimen for appropriate treatment. The disclosure does not provide any guidance towards the dosage regimen required to facilitate the treatment and/or prevention of the claimed disorders, nor indicate competent technical references in the appropriate methods.

Further, the instant claims are drawn not only to 'a method for treatment' but also to '**a method for prevention**', for which the specification does not provide sufficient enablement. 'To prevent' actually means *to anticipate* or *counter in advance, to keep from happening etc.* (as per Websters II Dictionary) and therefore it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the recited effect of **prevention**. Based on the MBR affinity, the

instant compounds are disclosed to be useful in the "prevention" of, for example, central nervous system diseases, etc., for which applicants provide no competent evidence. It is inconceivable from the *in vitro* data of a small number of representative compounds can be correlated to the "treating or **preventing**" of the various claimed disorders, such that the claimed compounds can not only treat but also "prevent" a myriad of diseases associated with the stated activity. Further, there is no evidence on record which demonstrates that the *in-vitro* screening test relied upon is recognized in the art as being reasonably predictive of success in any of the contemplated areas of "preventing". Such a reasonable correlation is necessary to demonstrate such utilities. See *Ex parte Stevens*, 16 USPQ 2d 1379 (BPAI 1990); *Ex parte Busse et al.*, 1 USPQ 2d 1908 (BPAI 1986) (the evidence must be accepted as "showing" such utility, and not "warranting further study").

Part of the difficulty of developing drugs effective for **preventing** any of the medical conditions such as central nervous system diseases, etc. lies in the lack of understanding as to why people come down with these disorders and the numerous causes of these disorders.

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements). This clearly highlights the unpredictability in the art and the need for undue experimentation. Furthermore, there is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disorders encompassed by the instant claims.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the

invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. In the claims, it is recited that many of the groups 'may have a **substituent(s)**', however, the claims do not provide what these 'substituent(s)' are intended to be. The specification provides some explanation and examples of the terms intended by the recitation 'substituent', however, it is recited that the terms defined therein 'may also have a substituent'. The definition is open ended and therefore, the scope of the term is not clear.
2. Claim 14 recites the limitation "... the compound represented by formula (Ib-1) according to claim 12, a salt thereof, an N-oxide thereof, a solvate thereof or a prodrug thereof" in lines 1-3. There is insufficient antecedent basis for this limitation in claim 12 on which claim 14 is dependent. Claim 12 does not recite the terms: "a salt thereof, an N-oxide

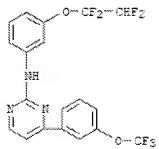
thereof, a solvate thereof or a prodrug thereof". The discrepancy is also appears in claims 19 and 20.

Claim Rejections - 35 USC § 102

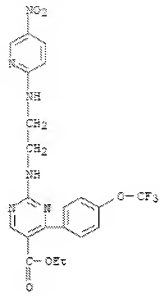
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

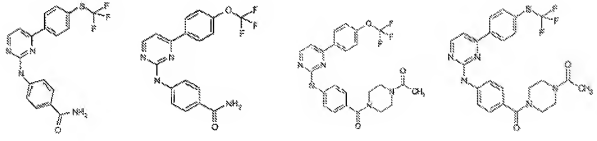
1. Claims 12 and 14-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Zimmermann, WO 95/09847. The instant claims read on reference disclosed compounds, see the compound of Example 2 (structure depicted below for convenience):



2. Claims 12 and 14-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Nuss et al., WO 99/65897. The instant claims read on reference disclosed compounds, see for example, the compound of Example 52 (structure depicted below for convenience):

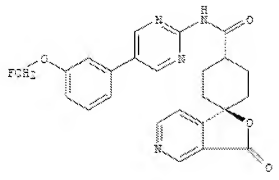


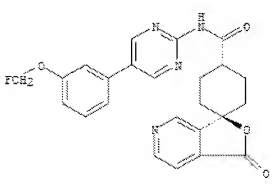
3. Claims 12 and 14-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Kois et al., WO 02/46170. The instant claims read on reference disclosed compounds, see for example, the compounds of Compound Numbers: 3-18 (page 31); 3-33 (page 35); 3-48 (page 40); 3-54 (page 42); etc. (structures depicted below for convenience):



4. Claims 12 and 14-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Fukami et al., US PGPub No. 2002/0188124. The instant claims read on reference disclosed compounds,

see for example, compound numbers: [191], [200] (page 11); etc. (structures depicted below for convenience):





Receipt is acknowledged of the Information Disclosure Statements filed on April 24, 2006; September 1, 2006 and March 16, 2007 and copies are enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Monday-Friday from 8:00am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Deepak Rao/
Primary Examiner
Art Unit 1624

September 10, 2009